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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/081,119	02/21/2002	Christoph Reinhard	PP-16932.002	8543

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EXAMINER	
VIVLEMORE, TRACY ANN	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 10/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/081,119	REINHARD ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) *6 and 8-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/02 and 9/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of group I, claims 1-5 and 7, in the reply filed on September 2, 2004 is acknowledged. The traversal is on the ground(s) that inclusion of the linking claim, claim 1, in each of groups I and II makes the restriction requirement improper as claim 1 is broader in scope than either of the embodiments of groups I or II. Applicant is correct that customarily the linking claim is not included in the listing of claims which embody each distinct invention and the restriction requirement would have been more clear if groups I and II were listed as containing claims 2-5 and 7. The inclusion of claim 1 into groups I and II was an inadvertent error and the examiner apologizes for any confusion this might have caused. However, claim 1 was clearly identified as a linking claim and the traversal of the restriction requirement on these grounds is not found persuasive because this argument does not address the propriety of the restriction between the patentably distinct inventions I-VII enumerated in the restriction requirement.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 6 and 8-34 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on September 2, 2004.

Claim Objections

3. Claim 1 is objected to because of the following informalities: in line 2 the word "redue" appears. This appears to be a typographic error that should be "reduce"; for the purposes of examination this word is interpreted to be "reduce". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 and 7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claim 1 is drawn to a method of reducing the growth of a cancerous cell by contacting the cell with an agent that is effective in reducing tyrosine threonine kinase (hereafter referred to as TTK) polypeptide activity. Claim 2 limits claim 1 by stating the reduction of TTK activity is a result of reduced TTK polypeptide levels while claim 3 states the agent is an antisense polynucleotide. Claim 4 limits claim 3 by stating the antisense polynucleotide is contained within a viral-based vector. Claim 5 limits claim 1

by stating the reduction of TTK activity is a result of a reduction of TTK polynucleotide levels. Claim 7 limits claim 5 by stating the TTK polypeptide has the sequence shown in SEQ ID NO: 2.

4. The specification teaches at page 4 that the instant invention features a method of inhibiting growth of a cancerous cell (and thereby treating the cancer) by introducing an antisense polynucleotide for inhibition of TTK expression. On page 8 possible modifications to base, sugar and phosphate linkages of the encompassed polynucleotides are described. Pages 8-9 also describe the sequences of the TTK genes that are targeted in the instant invention. On page 25, agents that modulate TTK activity are identified as being from numerous chemical classes, including small organic molecules, peptides, monoclonal antibodies, antisense polynucleotides, ribozymes, saccharides, fatty acids, steroids, purines or pyrimidines. Page 31 teaches that antisense polynucleotides are generally 20-3000 nucleotides in length and that SEQ ID NOS 1-12 constitute exemplary antisense polynucleotides. Administration and delivery methods are contemplated on pages 33-36. In example 2, it is shown that TTK is expressed differentially in many types cancer cells relative to expression in non-cancerous cells. Example 5 describes the effect of antisense polynucleotides on proliferation in three types of cancer cells while examples 6 and 7 describe the effect of antisense polynucleotides on colony formation and cell death.

5. The method of claim 1 encompasses the use of any type of agent that reduces TTK activity, including small molecules, antibodies, peptides and nucleic acids, including ribozymes or double stranded RNAs that act via an RNA interference

mechanism. The genus of claimed agents that reduce TTK activity is very large and the sequences of the antisense polynucleotides disclosed on page 31 as reducing TTK activity are not representative of the full breadth of this genus. Claim 3 is drawn to the embodiment of claim 1 wherein an antisense polynucleotide reduces TTK activity. However, the disclosed antisense sequences are not sufficient even to describe the sub-genus of antisense sequences to TTK, much less the full genus of nucleic acid agents that reduce TTK activity, including ribozymes or double stranded RNAs that act via an RNA interference mechanism. The disclosed antisense sequences also do not sufficiently describe the full breadth of the genus of agents that reduce TTK activity that are not nucleic acids. Inhibitors of a particular gene must be determined empirically and the antisense sequences provided do not share a common structure with the other classes of claimed molecules, such as antibodies, proteins or small molecules, that has been shown in the instant application or is known in the art to impart the function of reducing TTK activity. For example, there is no description of the structure of any nucleic acid that is a ribozyme or a double stranded RNA that acts via an RNA interference mechanism that reduces TTK activity. There is no description of the structures of any non-nucleic acid agents that reduce TTK activity; the list of candidate agents on page 25 contains no description of specific structures of agents known to reduce activity of TTK, only a wish list of chemical classes that might be included in the invention. The antisense sequences provided do not serve to describe these embodiments of the genus of agents that reduce TTK activity that are encompassed by the instant claims.

6. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

7. MPEP 2163 states in part, "An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004) (The patent at issue claimed a method of selectively inhibiting PGHS-2 activity by administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product, however the patent did not disclose any compounds that can be used in the claimed methods. While there was a description of assays for screening compounds to identify those that inhibit the expression or activity of the PGHS-2 gene product, there was no disclosure of which peptides, polynucleotides, and small organic molecules selectively inhibit PGHS-2. The court held that "[w]ithout such disclosure, the claimed methods cannot be said to have been described.")."

8. With the exception of the antisense sequences disclosed on page 31 of the specification, the skilled artisan cannot envision the detailed structure of the encompassed antisense sequences that reduce TTK activity or the encompassed

nucleic acids that reduce TTK activity that are not antisense polynucleotides. Also, the skilled artisan can not envision the detailed structure of the encompassed agents that reduce TTK activity that are peptides, small molecules, antibodies, saccharides, fatty acids, steroids, purines or pyrimidines, regardless of the complexity or simplicity of the method of isolation. There is no description of the structures of any non-nucleic acid agents that reduce TTK activity or any nucleic acids that reduce TTK activity that are not antisense nucleic acids. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

9. Therefore, only the disclosed antisense sequences, but not the full breadth of agents that reduce activity of TTK that are encompassed by the claimed methods meet the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Claims 1-5 and 7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for use of antisense polynucleotides to reduce

growth of cancer cells by reducing TTK activity *in vitro*, does not reasonably provide enablement for use of antisense polynucleotides to reduce growth of cancer cells by reducing TTK activity in any animal, including humans. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The following factors as enumerated *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), are considered when making a determination that a disclosure is not enabling: the breadth of the claims, the nature of the invention, the state of the prior art, the level of ordinary skill in the art, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples and the quantity of experimentation needed to make the invention based on the content of the disclosure.

Claim 1 is drawn to a method of reducing the growth of a cancerous cell by contacting the cell with an agent that is effective in reducing TTK polypeptide activity, which encompasses treatment of a cancer *in vitro* and in an organism. Claim 2 limits claim 1 by stating the reduction of TTK activity is a result of reduced TTK polypeptide levels while claim 3 states the agent is an antisense polynucleotide. Claim 4 limits claim 3 by stating the antisense polynucleotide is contained within a viral-based vector. Claim 5 limits claim 1 by stating the reduction of TTK activity is a result of a reduction of TTK polynucleotide levels. Claim 7 limits claim 5 by stating the TTK polypeptide has the sequence shown in SEQ ID NO: 2.

10. The specification teaches at page 4 that the instant invention features a method of inhibiting growth of a cancerous cell by introducing an antisense polynucleotide for inhibition of TTK expression. On page 8 the structure and possible modifications to base, sugar and phosphate linkages of the encompassed polynucleotides are described. Pages 8-9 also describe the TTK genes that are targeted in the instant invention. On page 25, agents that modulate TTK activity are identified as being from numerous chemical classes, including small organic molecules, peptides, monoclonal antibodies, antisense polynucleotides, ribozymes, saccharides, fatty acids, steroids, purines or pyrimidines. On page 31, antisense polynucleotides are described as being generally 20-3000 nucleotides in length and that SEQ ID NOS 1-12 constitute exemplary antisense polynucleotides. Administration and delivery methods are contemplated on pages 33-36. In example 2, it is shown that TTK is expressed differentially in many types cancer cells relative to non-cancerous cells. Example 5 describes the effect of antisense polynucleotides on proliferation in three types of cancer cells while examples 6 and 7 describe the effect of antisense polynucleotides on colony formation and cell death.

11. The instant specification discloses in examples 5-7 that reduction of TTK activity with antisense polynucleotides affects cancer cell proliferation and viability. There are no examples of any antisense polynucleotide being used to reduce TTK activity *in vivo* or to treat any type of cancer in any organism.

12. The state of the art prior art is such that inhibition of gene expression with antisense polynucleotides *in vitro* is routine, but *in vivo* inhibition of gene expression

using antisense polynucleotides at the time of filing and even to the present time is not routine for several reasons, including the problems of delivery, specificity and duration.

13. The problems of nucleic acid based therapies and antisense technology are well known in the art, particularly with regard to the inability to specifically deliver an effective concentration of a nucleic acid to a target cell, such that a target gene is inhibited to a degree necessary to result in a therapeutic effect. For example, at the time the instant invention was made, the therapeutic use of nucleic acids was a highly unpredictable art due to obstacles that continue to hinder the therapeutic application of nucleic acids *in vivo* (whole organism) (see for example Agrawal et al. (Molecular Medicine Today, 2000, vol 6, p 72-81), Branch (TIBS 1998, vol. 23, p. 45-50), and Jen et al. (Stem Cells 2000, Vol. 18, p 307-319)). Such obstacles include, for example, problems with delivery, target accessibility and the potential for unpredictable nonspecific effects.

14. Jen et al. state (see page 313, second column, second paragraph) "One of the major limitations for the therapeutic use of AS-ODNS and ribozymes is the problem of delivery....presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable". Jen et al. outlines many of the factors limiting the application of antisense for therapeutic purposes and concludes (see p 315, second column), "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive."

15. Opalinska et al. (Nature Reviews Drug Discovery, 2002, vol 1, p. 503-514) state "[I]t is widely appreciated that the ability of nucleic-acid molecules to modify gene expression *in vivo* is quite variable, and therefore wanting in terms of reliability. Several

issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells and identification of sequence that is accessible to hybridization in the genomic DNA or RNA" and in column 2 of the same page, "Another problem in this field is the limited ability to deliver nucleic acids into cells and have them reach their target. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient. As a general rule, oligonucleotides are taken up primarily through a combination of adsorptive and fluid-phase endocytosis. After internalization, confocal and electron microscopy studies have indicated that the bulk of the oligonucleotides enter the endosome-lysosome compartment, in which most of the material becomes either trapped or degraded."

16. Given this unpredictability, the skilled artisan would require specific guidance to practice the claimed methods *in vivo* in all organisms, with an inhibition of gene expression that would result in treatment of cancer, as claimed. The specification provides examples in human cancer cell lines and contemplates *in vivo* use, however, cell culture examples are generally not predictive of *in vivo* inhibition and the methods of delivery of the exemplified cell line would not be applicable to delivery of polynucleotides to any organism. Often formulations and techniques for delivery *in vitro* (cell culture) are not applicable *in vivo* (whole organism) (see for example Jen et al., page 313, second column, second paragraph). For example, Agrawal et al. (see p 79-80, section entitled "Cellular uptake facilitators for *in vitro* studies") states "The cellular uptake of negatively charged oligonucleotides is one of the important factors in determining the efficacy of antisense oligonucleotides.....*In vitro*, cellular uptake of

antisense oligonucleotides depends on many factors, including cell type, kinetics of uptake, tissue culture conditions, and chemical nature, length and sequence of the oligonucleotide. Any one of these factors can influence the biological activity of an antisense oligonucleotide." Due to differences in the physiological conditions of a cell *in vitro* versus *in vivo*, the uptake and biological activity observed *in vitro* would not predictably translate to *in vivo* results.

17. Given these teachings, the skilled artisan would not know *a priori* whether introduction of antisense polynucleotides *in vivo* by the broadly disclosed methodologies of the instant invention, would result in successful inhibition of cancer cell growth to a therapeutically significant extent. One of skill in the art would not know how to deliver polynucleotides to an organism in such a way that would ensure an amount sufficient to inhibit expression of TTK and reduce TTK polypeptide activity is delivered to the proper cell.

18. In fact, the state of the art is such that successful delivery of polynucleotide sequences *in vivo* or *in vitro*, such that the polynucleotide provides the requisite biological effect to the target cells/tissues/organs, must be determined empirically. Methods of inhibiting gene expression using nucleic acids *in vivo* are unpredictable with respect to delivery of the nucleic acid molecule such that the nucleic acid molecule is targeted to the appropriate cell/organ, at a bioeffective concentration and for a period of time such that the nucleic acid molecule is effective in, as in the instant application, inhibiting expression of TTK in order to reduce TTK polypeptide levels and reduce growth of a cancerous cell.

19. The specification does not provide the guidance required to overcome the art-recognized unpredictability of using antisense polynucleotides in therapeutic applications in any organism. The field of antisense therapeutics does not provide that guidance, such that the skilled artisan would be able to practice the claimed therapeutic methods.

20. Thus, while the specification is enabling for the inhibition of cancer cell growth *in vitro* as set forth in the specification, the specification is not enabling for the broad claims of treating cancer in all organisms with antisense polynucleotides as the art of inhibiting gene expression by introducing antisense polynucleotides into an organism is neither routine nor predictable. In order to practice the claimed invention *in vivo* in all organisms a number of variables would have to be optimized, including 1). determining what sequences would constitute antisense sequences capable of binding to TTK and what antisense sequences would actually bind to TTK and form a strong enough complex that they would be effective at inhibiting expression of TTK and reducing TTK polypeptide levels, 2). the form of the antisense polynucleotide, whether to use a modified polynucleotide with one or more backbone, sugar or base modifications, 3). the mode of delivery of the antisense polynucleotide to an organism that would allow it to reach the targeted cell, 4). the amount of antisense polynucleotide that would need to be delivered in order to bind a sufficient amount of TTK to inhibit expression of TTK and reduce TTK polypeptide levels once it reached the proper cell and 5). ensuring the antisense polynucleotide remains viable in a cell for a period of time that allows inhibition of expression of TTK to an extent that there is a measurable and significant

therapeutic effect. Each one of these variables would have to be empirically determined for each antisense polynucleotide. While optimization of any single one of these steps may be routine, when taken together the amount of experimentation required becomes such that one of skill in the art could not practice the invention commensurate in scope with the claims without undue, trial and error experimentation and therefore, claims 1-5 and 7 are not enabled.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:45-5:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Tracy Vivlemore
Examiner
Art Unit 1635

TV
October 20, 2004

SEAN McGARRY
PRIMARY EXAMINER